UNIVERSITY OF PENNSYLVANIA

MORPHINE STUDIES
THE SYNTHESIS OF A GROUP OF COMPOUNDS BEARING STRUCTURAL SIMILARITIES TO MORPHINE

A DISSERTATION

IN CHEMISTRY

PRESENTED TO THE FACULTY OF THE GRADUATE SCHOOL IN

PARTIAL FULLFILMENT OF THE REQUIREMENTS FOR

THE DEGREE OF DOCTOR OF PHILOSOPHY

RICHARD U. SCHOCK, JR.

PHILADELPHIA

1948

Diss. Philadelphia
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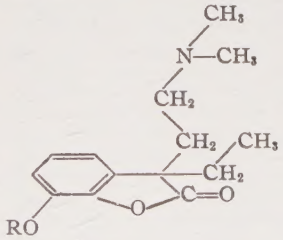
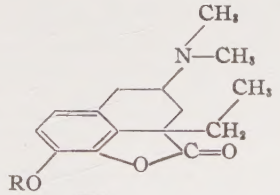
Morphine Studies. 2-Keto-7-methoxy-2,3-dihydrobenzofuran Derivatives[1]

By R. U. Schock, Jr[2,3]

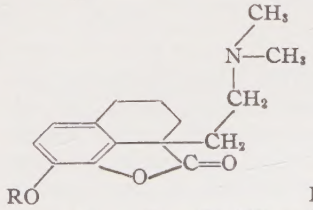
From an examination of the structure of synthetic compounds (Demerol and Amidone series) which possess physiological activity similar to that of morphine (I), it is apparent that some of the functional groups and rings of morphine do not play an important role in providing the type of activity which morphine displays. All have in common a quaternary carbon adjacent to an aromatic nucleus and a tertiary nitrogen in a β-relationship to this carbon, but a phenanthrene system is evidently not necessary. In investigating further the problem of the relation between structure and physiological activity in the morphine series, the synthesis of four model compounds has been planned (II, III, IV, V). Each of these derivatives



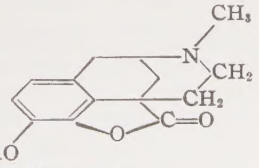
II



III



IV R = H, CH_3 or $COCH_3$



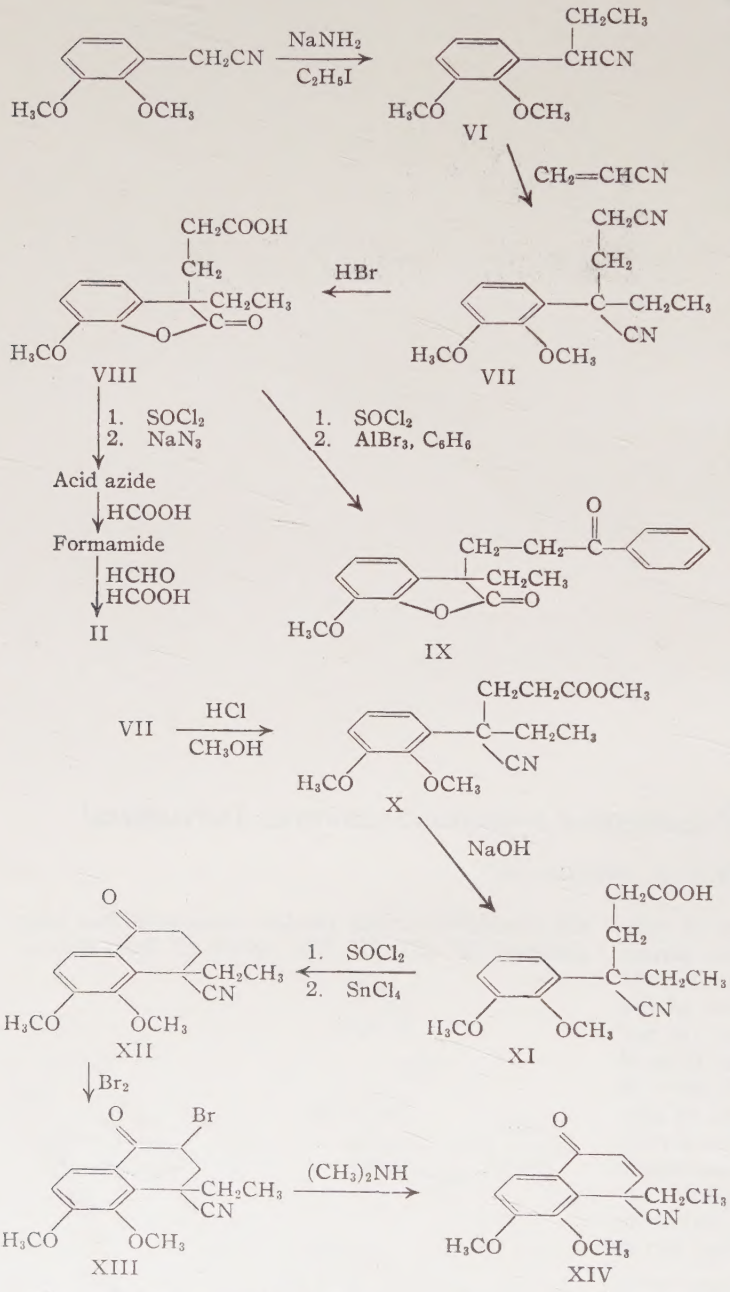
V

(1) Presented before the Division of Organic Chemistry, Second Meeting in Miniature of the Philadelphia Section of the American Chemical Society, Philadelphia, Pa., January 22, 1948.

(2) Abstracted from the thesis of R. U. Schock, Jr., presented to the Faculty of the Graduate School of the University of Pennsylvania in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(3) Bristol Laboratories Fellow, 1946–1947; National Institute of Health Fellow, 1947–1948.

tives duplicates, in part, what is considered to be essential portions of the morphine molecule and each compound successively approaches more closely to the structure of morphine. This paper reports the synthesis of II, an open-chain analog, and some of the routes explored for the preparation of III, a tetralin analog.



The starting material for these syntheses was 2,3-dimethoxyphenylacetonitrile.[4] Sodamide alkylation of this compound with ethyl iodide served to introduce the ethyl side-chain, and the product (VI) added acrylonitrile to form the dinitrile VII. It was found that by a short reflux period with 48% hydrobromic acid it was possible to demethylate only the *ortho* methoxyl group of VII. At the same time both cyano groups were hydrolyzed and cyclization to the lactone-acid VIII occurred. The carboxyl group was then converted by the Curtius method to a formylated amino group by decomposing the acid azide in the presence of formic acid. This formamide was alkylated with a mixture of formalin and formic acid[5] to yield II as a crystalline solid.

Numerous attempts were made to obtain a tetralin-lactone structure by cyclization of the acid chloride of VIII under the usual conditions for intramolecular acylation. Under mild conditions, in the presence of aluminum chloride, aluminum bromide or stannic chloride, the acid chloride or acid was recovered unchanged. More vigorous conditions usually led to destruction of the compound. With aluminum bromide in benzene as a solvent, the ketone IX was isolated in good yield. The failure of these cyclization experiments is believed to be due to steric limitations imposed by the lactone ring.

Experiments were then directed toward formation of the tetralin system prior to lactonization. The α-bromoketone XIII was prepared without difficulty, but reaction with dimethylamine at room temperature led to the unsaturated ketone XIV in practically quantitative yield.

Further studies are underway on possible routes to tetralin-lactone structures and these results will be reported later.

Acknowledgment.—We are indebted to Miss Sarah H. Miles for the analyses.

Experimental

All melting points are corrected.

α-(2,3-Dimethoxyphenyl)-butyronitrile (VI).—Sodamide was prepared by the reaction of 12.7 g. (0.55 mole) of sodium and 400 ml. of liquid anhydrous ammonia in the presence of a trace of ferric nitrate.[6] A solution of 88.5 g. (0.50 mole) of 2,3-dimethoxyphenylacetonitrile in 100 ml. of dry benzene and 100 ml. of dry ether was added to the suspension of sodamide in the liquid ammonia. The suspension was stirred for one hour or until the ammonia had evaporated. Then, with vigorous stirring, a mixture of 100 ml. of ethyl iodide and 100 ml. of dry ether was added at such a rate that the heat of reaction maintained

(4) Horning, and Platt, *J. Am. Chem. Soc.*, **69**, 2929 (1947).

(5) The fact that aldehydes, in the presence of formic acid, alkylate certain acylated amines was contributed by E. C. Wagner and Ezra Staple and is, in part, the subject of a doctoral dissertation undertaken by Mr. Staple.

(6) "Organic Syntheses," **25**, 25 (1945).

the mixture at gentle reflux. After heating under reflux for one hour the mixture was cooled and diluted with 500 ml. of cold water. The layers were then separated and the aqueous phase extracted once with 100 ml. of ether. The combined organic solutions were washed successively with water and 1% acetic acid and dried over magnesium sulfate. The ether and benzene were distilled leaving a residue which was fractionated through a short Vigreux column. There was obtained, after a small forerun consisting principally of unchanged starting material, 86.0 g. (84%) of product boiling at 171–181° (23 mm.). Redistillation gave a sample for analysis as a pale yellow oil boiling at 178–179° (23 mm.); $n^{25}D$ 1.5157.

Anal. Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37. Found: C, 70.31; H, 7.40.

α-Ethyl-α-(2,3-dimethoxyphenyl)-glutaronitrile (VII).—The procedure followed was essentially that of Bruson[7] for the cyanoethylation of phenylacetonitrile. A solution of 30.8 g. (0.15 mole) of the nitrile VI in 40 ml. of *t*-butyl alcohol was heated to 40° and then, with stirring, the dropwise addition of a solution of 16 g. of acrylonitrile in 15 ml. of *t*-butyl alcohol was begun. After the addition of a few drops, 1.0 g. of 30% methyl alcoholic potassium hydroxide was added and the temperature maintained at 40–45° by occasional external cooling. Another gram of catalyst was introduced after half the acrylonitrile was added. When the heat of reaction was no longer evident, the solution was heated for one hour at 40–45° and allowed to stand overnight. The dark solution was acidified with dilute hydrochloric acid and diluted with 250 ml. of cold water. The layers were separated with the aid of ether and the aqueous layer extracted once with 50 ml. of ether. Occasionally the mixture contained a small amount of an insoluble solid which was removed by filtration prior to separation of the layers. The combined extracts were washed with water and dried over magnesium sulfate. Distillation of the residue after evaporation of the solvent yielded three fractions: 4–5 g. of a colorless liquid boiling at 80–85° (21 mm.) which was not investigated, 7.6 g. of starting material boiling at 135–145° (4 mm.), and 26.2 g. of product boiling at 193–200° (3 mm.).

Based on unrecovered starting material, the yield was 87%. The pure compound was a pale yellow viscous oil, b. p. 190–191° (2 mm.).

Anal. Calcd. for $C_{15}H_{18}O_2N_2$: C, 69.74; H, 7.02. Found: C, 69.94; H, 6.95.

2-Keto-3-ethyl-3-(β-carboxyethyl)-7-methoxy-2,3-dihydrobenzofuran (VIII).—A solution of 10.8 g. of the dinitrile (VII) in a mixture of 50 ml. of glacial acetic acid and 70 ml. of 48% hydrobromic acid was boiled under reflux for thirty minutes. The hot solution was diluted with water to the cloud point and chilled overnight, yielding 5.6 g. of colorless prisms melting at 132–134°. The filtrate was extracted with four 40-ml. portions of a mixture of benzene and ether (1:3), and the combined extracts were washed with 50 ml. of a saturated sodium bicarbonate solution. Acidification of the bicarbonate extract yielded an oil which crystallized when seeded. The combined yield of crude product was 8.5 g. (78%). Two recrystallizations from dilute ethanol yielded an analytical sample, m. p. 136–137°.

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10. Found: C, 63.85; H. 6.37.

The rate of demethylation of the methoxyl groups in compound VII is sufficiently different to permit the isolation of the acid VIII in good yield, but the experimental conditions must be adjusted with care. Shorter reaction periods led to lowered yields and recovered dinitrile; longer reaction periods or more vigorous conditions also led to lowered yields, presumably because of further demethylation. The phenol-acid corresponding to the lactone VIII was not isolated.

The **anilide** of the acid VIII was prepared by conversion to the acid chloride with thionyl chloride, followed by reaction with aniline. Recrystallization from dilute ethanol yielded a colorless sample, m. p. 122–123°.

Anal. Calcd. for $C_{20}H_{21}O_4N$: C, 70.78; H, 6.23; N, 4.13. Found: C, 70.75; H, 6.32; N, 3.93.

2-Keto-3-ethyl-3-(β-dimethylaminoethyl)-7-methoxy-2,3-dihydrobenzofuran (II).—To a suspension of 14.2 g. (0.054 mole) of crude VIII in 20 ml. of dry ether, was added 10 ml. of thionyl chloride and one drop of pyridine. After standing for fifteen hours the volatile constituents were removed under reduced pressure at 50° and the residue dissolved in 50 ml. of dry reagent-grade acetone.[8] The acetone solution was then chilled in an ice-bath and, with vigorous stirring, a solution of 4.0 g. (0.060 mole) of sodium azide in 11 ml. of water was added over a period of one minute. After stirring for fifteen minutes, 200 ml. of cold water was added and the crude azide extracted with two 75-ml. portions of benzene. The extract was washed once with 50 ml. of a saturated solution of sodium bicarbonate and then dried for fifteen minutes over magnesium sulfate. The dried solution was concentrated to about 40 ml. The flask was then provided with a reflux condenser and 15 ml. of 98–100% formic acid added cautiously to the hot solution. The rearrangement is accompanied by considerable frothing and evolution of gas and care must be exercised in controlling the reaction. After refluxing for thirty minutes, the benzene and formic acid were removed by distillation and the residue boiled under reflux for 16 hours with 20 ml. each of 35% formalin solution and 90% formic acid. The dark solution was diluted with 100 ml. of 5% hydrochloric acid solution and extracted once with 75 ml. of ethyl acetate; it was then made alkaline by the addition of solid sodium bicarbonate. The alkaline solution was extracted with four 50-ml. portions of ethyl acetate and the residue remaining after evaporation of the solvent evaporatively distilled. There was obtained 6.9 g. of product (48% based on VIII) distilling at 110–115° (0.1 mm.). The product crystallized on standing and was purified by recrystallization from cyclohexane; the melting point was 66–67°.

Anal. Calcd. for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.04. Found: C, 68.43; H, 7.93.

The **picrate**, prepared in the usual fashion, melted at 183–184° after one recrystallization from absolute ethanol.

Anal. Calcd. for $C_{15}H_{21}O_3N \cdot C_6H_3O_7N_3$: C, 51.22; H, 4.91. Found: C, 51.06; H, 4.74.

The **hydrochloride** was prepared by the addition of concentrated hydrochloric acid to a concentrated solution of the amine in ethanol and allowing the precipitated crystals to stand *in vacuo* over potassium hydroxide pellets and concentrated sulfuric acid. The pure salt melted at 216–217° after recrystallization from methyl isobutyl ketone.

Anal. Calcd. for $C_{15}H_{22}O_3NCl$: C, 60.09; H, 7.40; N, 4.67. Found: C, 59.92; H, 7.39; N, 4.59.

Attempts to Cyclize the Acid Chloride of VIII.—Employment of stannic chloride in benzene solution following the usual procedure[9] led to recovery of unchanged acid chloride and some of the original acid. With either aluminum chloride or aluminum bromide in carbon disulfide, the products ranged from intractable resins to starting material depending upon the temperature at which the reaction was run. When the following procedure was employed, using benzene as a solvent, the ketone IX was formed.

A mixture of 3.0 g. of VIII and 6 ml. of thionyl chloride was allowed to stand overnight. The excess thionyl chloride was removed at 50° at the water pump, the last traces being removed by the addition of 2 ml. of dry benzene and again evaporating the solvent. The residue was taken up in 50 ml. of dry thiophene-free benzene and the resultant solution chilled to the freezing point; a solution of 6.6 g. of aluminum bromide in 15 ml. of benzene was then added and the mixture allowed to stand at room tem-

(7) Bruson and Riener, *J. Am. Chem. Soc.*, **65**, 23 (1943).

(8) The so-called "wet method" of preparing azides is that found in "Organic Reactions," Vol. III, 387 (1946).

(9) "Organic Reactions," Vol. II, 1944, p. 138.

perature for forty-five minutes. The dark solution was poured on a mixture of ice and 10 ml. of concentrated hydrochloric acid and, after standing for fifteen minutes, the mixture was steam distilled. The oily residue was separated from the aqueous phase by means of 50 ml. of ether, and the extract washed successively with 5% hydrochloric acid, water, 2% sodium hydroxide solution, 1% acetic acid and finally water; the solution was then dried over magnesium sulfate. Evaporation left 2.5 g. of a pale brown oil which crystallized on standing. Three recrystallizations from methanol yielded colorless diamond-shaped prisms of 2-keto-3-ethyl-3-(β-benzoylethyl)-7-methoxy-2,3-dihydrobenzofuran (IX), m. p. 89–90°.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.21. Found: C, 74.19; H, 5.95.

The **2,4-dinitrophenylhydrazone** was obtained as an orange powder, m. p. 204–205° (recrystallized from ethyl acetate–ethanol).

Anal. Calcd. for $C_{26}H_{24}O_7N_4$: C, 61.90: H, 4.80. Found: C, 61.79; H, 4.68.

4-Ethyl-4-cyano-5,6-dimethoxytetralone-1 (XII).—The intermediate acid XI necessary for the cyclization was obtained by hydrolysis of the cyanoester X. The dinitrile VII (9.8 g.) was dissolved in 100 ml. of absolute methanol. Dry hydrogen chloride was passed rapidly into the solution for fifteen minutes and the mixture was heated gently under reflux for one hour. Two-thirds of the alcohol was removed by distillation or evaporation, the residue was diluted with water and the nitrile-ester separated with ether. The ether was evaporated leaving a residue of **methyl γ-(2,3-dimethoxyphenyl)-γ-cyano-caproate (X)**. A small sample of the ester was purified for analysis by evaporative distillation at 105–115° (0.06 mm.). It was a pale yellow oil.

Anal. Calcd. for $C_{16}H_{21}O_4N$: C, 65.96; H, 7.27. Found: C, 66.04; H, 7.04.

The ester was saponified by heating under reflux for one hour with a solution of 3.5 g. of sodium hydroxide in 75 ml. of water and 25 ml. of ethanol. Dilution of the cooled solution produced a cloudy appearance which disappeared upon extraction with ether. On acidification with dilute hydrochloric acid, a pale yellow oil precipitated which was separated by two 50-ml. portions of ether. The ether extract was dried and then evaporated, leaving a residue consisting of 9.7 g. (92%) of the acid-nitrile XI as an oil. The product was not purified further, but it was characterized by conversion of a small sample to the *p*-bromophenacyl ester, m. p. 104–105° (from dilute methanol).

Anal. Calcd. for $C_{23}H_{24}O_5NBr$: C, 58.23; H, 5.10. Found: C, 58.31; H, 4.70.

Thionyl chloride (20 ml.) was added cautiously to 9.7 g. of the acid-nitrile XI and the solution allowed to stand overnight. The excess thionyl chloride was removed at 50° at the water pump; 5 ml. of dry benzene was added and the operation repeated. The residue was taken up in 150 ml. of dry thiophene-free benzene and the solution was chilled until the benzene began to crystallize. A solution of 15 ml. of stannic chloride in 15 ml. of benzene was added with shaking and the mixture allowed to stand at room temperature for one hour. The yellow complex was decomposed by pouring upon a mixture of ice, 30 ml. of concentrated hydrochloric acid and 30 ml. of ether. The organic layer was washed successively with 5% hydrochloric acid, water, 5% sodium hydroxide solution and water and dried over magnesium sulfate. Removal of the ether left 8.6 g. of nearly colorless oil which crystallized to a solid melting at 116–118°. The yield of tetralone based on the acid-nitrile was 95%; the over-all yield based on the dinitrile VI was 88%. Recrystallization from cyclohexane yielded colorless prisms melting at 118–118.5°.

Anal. Calcd. for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61. Found: C, 69.37; H, 6.45.

The 2,4-dinitrophenylhydrazone crystallized from benzene as a dark maroon powder, m. p. 250–251°.

Anal. Calcd. for $C_{21}H_{21}O_6N_5$: C, 57.39; H, 4.82. Found: C, 57.50; H, 4.68.

The procedure for hydrolysis of the dinitrile was developed after direct hydrolysis failed to give satisfactory results.

2-Bromo-4-ethyl-4-cyano-5,6-dimethoxytetralone-1 (XIII).—One gram of the ketone XII was dissolved in 35 ml. of absolute ether. A few drops of a solution of 0.62 g. of bromine in 5 ml. of chloroform was added at room temperature; after decolorization the remainder was added dropwise at 10° slowly enough so that at no time was there an appreciable excess of free bromine. The solution was washed with 5% sodium hyroxide solution and then with water. Drying, followed by evaporation, left 1.30 g. (99%) of a colorless crystalline residue which melted at 141–143°; two recrystallizations from ethanol raised the melting point to 143–144°.

Anal. Calcd. for $C_{15}H_{16}O_3NBr$: C, 53.27; H, 4.77. Found: C, 53.25; H, 4.69.

When brominations were carried out on a larger scale a dibromo derivative was isolated in small quantity by precipitating the monobromo compound from a concentrated benzene solution with petroleum ether, the disubstituted product remaining in solution. It was recrystallized from methanol and melted at 137–138°.

Anal. Calcd. for $C_{15}H_{15}O_3NBr_2$: C, 43.29; H, 3.87. Found: C, 43.53; H, 3.69.

Reaction of XIII with Dimethylamine to Form XIV.—The bromoketone (1.0 g.) was allowed to stand at room temperature in 40 ml. of dry benzene containing 5 equivalents of dimethylamine. After twenty-four hours the solution was washed with two 40-ml. portions of water, once with 40 ml. of 5% hydrochloric acid solution and then with water. Drying over magnesium sulfate followed by evaporation of the solvent left 0.76 g. (100%) of a crystalline residue. This product melted at 132–133° after two recrystallizations from cyclohexane.

Anal. Calcd. for $C_{15}H_{15}O_3N$: C, 70.02; H, 5.88. Found: C, 70.15; H, 5.66.

The **2,4-dinitrophenylhydrazone** was crystallized from benzene and melted at 271° (dec.).

Anal. Calcd. for $C_{21}H_{19}O_6N_5$: C, 57.66; H, 4.38; Found: C, 57.67; H, 4.34.

Summary

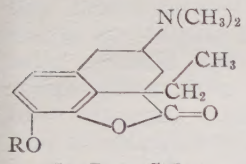
The synthesis of 2-keto-3-ethyl-3-(β-dimethylaminoethyl)-7-methoxy-2,3-dihydrobenzofuran is described.

Preliminary experiments directed toward the synthesis of 8-hydroxy-7-methoxy-3-dimethylamino-1-ethyl-1-carboxy-1,2,3,4-tetrahydronaphthalene lactone (III) are also described.

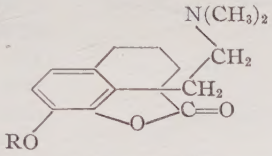
Morphine Studies. Tetralin Analogs[1]

By R. U. Schock, Jr.[2]

In a previous paper[3] several unsuccessful routes directed to the preparation of 1-ethyl-1-carboxy-3 - dimethylamino - 7 - methoxy - 8 - hydroxy - 1,2,3,4-tetrahydronaphthalene lactone (Ia) were described. The synthesis of the corresponding 7-acetoxy lactone Ib has now been accomplished by the method described in this report. In addition, experiments directed toward the synthesis of an isomeric lactone, 1-carboxy-1-(β-dimethylaminoethyl) - 7 - acetoxy - 8 - hydroxy - 1,2,3,4 - tetrahydronaphthalene lactone (II) have been carried out. It was our original intention to compare analgesic properties in a series of lactones, but the unexpected instability of the lactone Ib

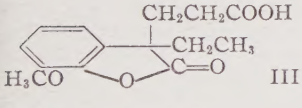


Ia, R = CH_3
Ib, R = $COCH_3$

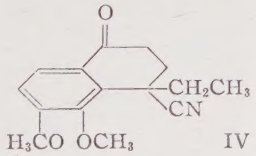


II, R = $COCH_3$

has made this impossible. The failure of cyclization experiments with 2-keto-3-ethyl-3-(β-carboxyethyl) - 7 - methoxy - 1,2 - dihydrobenzofuran (III), together with the successful cyclization of γ-(2,3-dimethoxyphenyl)-γ-cyanocaproyl chloride to 4-cyano-4-ethyl-5,6-dimethoxytetralone-1 (IV),[3] indicated that the desired lactone structures (Ia or Ib and II) very likely constituted strained systems. The steric effect of a lactone system such as that of III in preventing cyclization to a tetralone has apparently not been encountered previously, but as a result of this effect it is evident that compounds I and II can probably be obtained only from appropriate tetralin precursors.



III



IV

For the synthesis of Ib, the starting material was methyl γ-(2,3-dimethoxyphenyl)-γ-cyanocaproate.[3] By condensation with ethyl formate and sodium methoxide, the expected hydroxymethylene compound (VI) was obtained. This was cyclized to the dihydronaphthalene VII with a mixture of sulfuric and phosphoric acids; the resulting ester was saponified to the corresponding acid, and the unsaturated bond reduced by catalytic means (palladium–carbon) to give 1-cyano-1 - ethyl - 7,8 - dimethoxy - 1,2,3,4 - tetrahydro - 3-naphthoic acid (VIII). The over-all yield for these four steps was about 70%. The carboxylic acid group of compound VIII was converted into a dimethylamino group by a combination of the Curtius procedure and a formaldehyde–formic acid methylation; the yield for this conversion was 64%. The resulting amine IX was treated with hydrobromic acid under reflux, and the crude acid obtained in this way was heated with acetic anhydride and sodium acetate to form the lactone Ib.

This lactone was stable only in the absence of water, and only one stable derivative (a methiodide) could be obtained. On standing in the open for one week, or for a few hours in the presence of water, the liquid lactone was transformed to the crystalline amino acid X. The instability of this lactone is not unusual in the light of the behavior of intermediates in this series, and it is apparently due to strain in the fused tricyclic system. The fused-ring system of morphine includes a tetralin–furan system, and it is possible that a similar strain exists in the morphine molecule.

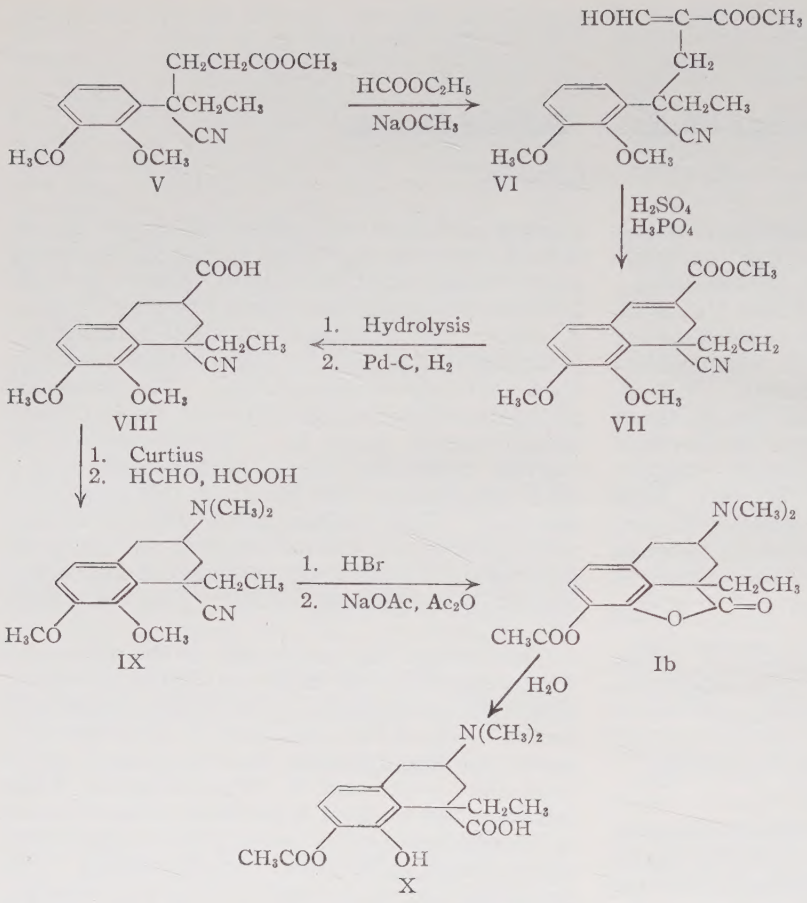
The experimental work for the proposed synthesis of the isomeric lactone II entailed first the addition of two moles of acrylonitrile to 2,3-dimethoxyphenylacetonitrile. The resulting product, γ-cyano - γ - (2,3 - dimethoxyphenyl) - pimelonitrile (XI), was converted into the lactone XIX by treatment with hydrobromic acid. In general, it has been found in this series that a short reflux period with hydrobromic acid results in the selective cleavage of the 2-methoxyl group, with hydrolysis of the nitrile group occurring at the same time. If, however, related tetralin derivatives are subjected to approximately the same conditions, the hydrolysis of the tertiary nitrile group is accompanied by cleavage of both methoxyl groups. Attempts were made to cyclize the di-acid chloride from the lactone XIX to a tetralone, but without success. This behavior is the same as that exhibited by the lactone-acid III.

The tetralone XIII was obtained without difficulty in 81% yield by cyclization with stannic chloride of the di-acid chloride obtained from the acid XII. No evidence of intermolecular acylation was found. The required acid was obtained by a two-step hydrolysis procedure from the trinitrile XI. The trinitrile was converted to a dimethyl ester with methanol and hydrogen chloride, and saponification with aqueous alkali

(1) Abstracted from the dissertation of R. U. Schock, Jr., presented to the faculty of the Graduate School of the University of Pennsylvania in partial fulfilment of the requirements for the degree of Doctor of Philosophy, April, 1948.

(2) Bristol Laboratories Fellow, 1946–1947; National Institute of Health Fellow, 1947–1948.

(3) For a discussion of the objectives of these studies, see Horning and Schock, *J. Am. Chem. Soc.*, **70**, 2941 (1948).



yielded the dicarboxylic acid. This procedure was developed after direct alkaline hydrolysis failed to give the desired product.

The reduction of the carbonyl group of the tetralone XIII to a methylene group presented a problem which could not be solved in satisfactory fashion. With the Clemmensen method, the initial step was hydrolysis to the cyclic imide XVII. In separate experiments, it was found that hydrolysis and cyclization to the imide occurred with surprising ease in an acetic acid–hydrochloric acid mixture. It was possible in turn to hydrolyze the imide to an amide-acid with warm dilute alkali (the structure XVIII has been assigned to this compound), but Clemmensen reductions starting with XII or XVII were unsuccessful. The improved Wolff–Kishner technique[4] gave a small amount of the tetralin XIV. It is interesting to note that the 4-cyano group in this compound is easily attacked under acid conditions, but a small amount of material survived the vigorous alkaline conditions of the Wolff–Kishner method with this group unchanged. An attempt was made to improve the yield by using the imide XVII in this method, but without success. The best means found for the reduction was catalytic hydrogenation with a palladium–carbon catalyst at 50–60° in acetic acid in the presence of a little sulfuric acid. Unfortunately, the course of the reaction was difficult to control and the yields were not reproducible. The products were always impure, and it is believed that reduction also took place at other points in the molecule. Through repetition of the reaction, it was possible to obtain a small amount of material, and the remaining steps were attempted. It was found that the carboxyl group could be converted into a dimethylamino group according to the same procedure used in the synthesis of Ib, in about 40% yield. The next reaction, hydrolysis with hydrobromic acid, was less successful, and it was not possible to isolate the expected lactone after treatment with acetic anhydride–sodium acetate. In view of the difficulty in preparing XIV, and the fact that the lactone II, if obtained, might be expected to be unstable, no further attempt has been made to investigate the last steps in this sequence.

Acknowledgment.—The authors are indebted to Miss Sarah H. Miles for the analyses.

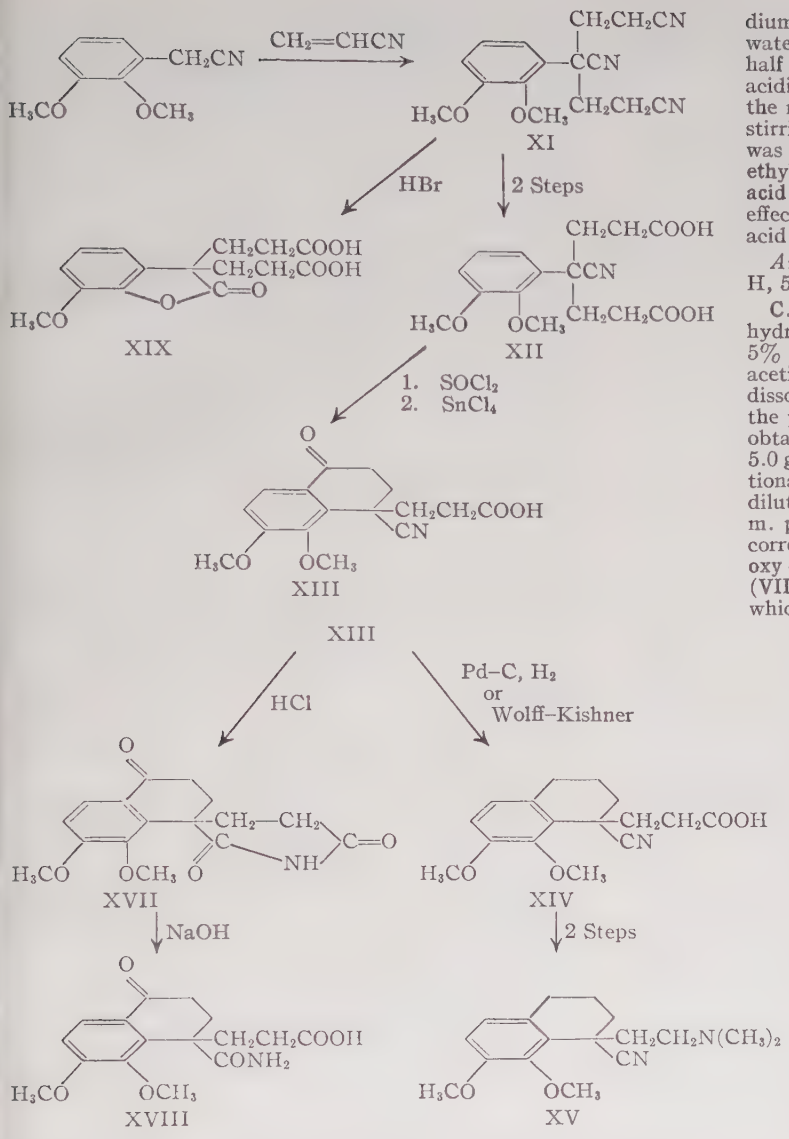
Experimental

All melting points are corrected.

1-Cyano-1-ethyl-7,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthoic Acid (VIII). A. Formylation.—The following procedure was adopted after decreased yields were encountered using either methyl formate or sodium ethoxide in the condensation. A solution of 49.5 g. (0.17 mole) of methyl γ-(2,3-dimethoxyphenyl)-γ-cyanocaproate[3] (V) and 25.0 g. (0.34 mole) of ethyl formate in 50 ml. of dry ether was added at room temperature to a suspension of sodium methoxide in 100 ml. of dry ether. The sodium methoxide was obtained from the reaction of 7.8 g. (0.34 mole) of sodium and absolute methanol, with evaporation of the excess alcohol on the steam-bath at the water pump. After stirring for one and one-half hours, a second portion of 25.0 g. of ethyl formate was added and the stirring continued for an additional hour. At this time all suspended material had dissolved. After standing for fifteen hours, 300 ml. of ice water was added and the layers separated. The aqueous phase was washed once with 100 ml. of ether, acidified with dilute acetic acid, and extracted with two 100-ml. portions of ether. The latter extract was washed once with saturated sodium bicarbonate solution, dried and the ether evaporated. There was obtained 47.9 g. (*ca.* 88%) of the hydroxymethylene derivative. The first extract yielded 3–4 g. of unreacted ester, pure enough for use in further condensations.

B. Cyclization.—The hydroxymethylene compound (16.7 g.) was dissolved in 20 ml. of glacial acetic acid, and this solution was then added to a mixture of 55 ml. of 85% phosphoric acid and 12 ml. of concentrated sulfuric acid,

(4) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).



keeping the temperature below 0°. After standing with occasional stirring for thirty minutes at −5°, the flask was removed from the freezing bath and allowed to stand at room temperature for one and one-half hours. A colorless viscous gum separated on pouring upon ice; this was extracted with three 75-ml. portions of ether. Usually the addition of ether caused the separation of a small amount of a crystalline solid, m. p. 131–135°, which proved to be **methyl 1-cyano-1-ethyl-7,8-dimethoxy-1,2-dihydro-3-naphthoate (VII)**. Purification by recrystallization from ethyl acetate–petroleum ether (b. p. 35–60°) raised the melting point to 135–136°.

Anal. Calcd. for $C_{17}H_{19}O_4N$: C, 67.75; H, 6.36. Found: C, 67.60; H, 6.18.

It is believed that the amorphous material obtained here is a mixture of ethyl and methyl esters formed by ester interchange between ethyl formate and V. The viscous material solidified on standing but it was not possible to isolate a single, pure compound by recrystallization.

The combined ether extracts were washed once with 50 ml. of 5% sodium hydroxide solution and once with water. The residue remaining after evaporation of the ether was combined with the solid ester which separated, and the mixture boiled under reflux with a solution of 6.0 g. of sodium hydroxide in a mixture of 150 ml. of water and 30 ml. of ethanol for one and one-half hours. The hot alkaline solution was acidified with dilute hydrochloric acid and the mixture allowed to stand with occasional stirring until crystallization ensued. There was obtained 11.9 g. (79%) of **1-cyano-1-ethyl-7,8-dimethoxy-1,2-dihydro-3-naphthoic acid** as a colorless solid. Purification was effected by recrystallization from dilute acetic acid; m. p. 186–187°.

Anal. Calcd. for $C_{16}H_{17}O_4N$: C, 66.88; H, 5.96. Found: C, 66.84; H, 5.76.

C. Reduction.—The unsaturated acid was hydrogenated at atmospheric pressure over 5% palladium–carbon catalyst[5] in glacial acetic acid at 65°. From 5.0 g. of the acid dissolved in 50 ml. of glacial acetic acid, in the presence of 1.5 g. of catalyst, there was obtained upon evaporation of the solvent, 5.0 g. of product melting at 158–165°. Fractional crystallization from either benzene or dilute acetic acid resulted in a compound, m. p. 183–184°, which gave analytical data corresponding to **1-cyano-1-ethyl-7,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthoic acid (VIII)**. There are two diastereoisomers which might result from this reaction, but a second crystalline compound could not be isolated from the filtrates after crystallization of VIII.

Anal. Calcd. for $C_{16}H_{19}O_4N$: C, 66.42; H, 6.62. Found: C, 66.38; H, 6.48.

1-Cyano-1-ethyl-3-dimethylamino-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (IX).—The acid VIII (10.0 g.), without previous recrystallization, was allowed to stand in the presence of 10 ml. of thionyl chloride for a period of fifteen hours. The excess thionyl chloride was removed at the water pump at 50° and the residue dissolved in 50 ml. of dry reagent-grade acetone. With vigorous stirring, a solution of 2.6 g. of sodium azide in 8 ml. of water was added to the chilled solution of the acid chloride over a period of approximately one minute. After fifteen minutes the mixture was diluted with 150 ml. of cold water, and the crude azide was separated with three 50-ml. portions of benzene. The combined extracts were washed once with saturated sodium bicarbonate solution and then dried for fifteen minutes over magnesium sulfate. The dried solution was concentrated to a volume of approximately 50 ml. and then 10 ml. of 98–100% formic acid was added cautiously to the hot solution. After the exothermic reaction and the copious frothing subsided, the solution was heated under reflux for one hour, and then the volatile constituents were removed in a current of air at steam-bath temperature. The residue was dissolved in a mixture of 20 ml. of 90% formic acid and 20 ml. of 35% formalin solution and boiled under reflux for twenty hours or until the evolution of carbon dioxide had practically ceased. To the chilled solution was added 100 ml. of 5% hydrochloric acid, and it was then extracted with 100 ml. of ethyl acetate. After neutralizing the aqueous phase with solid sodium bicarbonate, it was extracted with four 75-ml. portions of ethyl acetate. Evaporative distillation at 145–155° (0.2 mm.) of the residue remaining after removal of the solvent gave 6.4 g. of product (64%) as a viscous, somewhat opalescent oil.

Anal. Calcd. for $C_{17}H_{24}O_2N_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.81; H, 8.32; N, 9.55.

(5) "Organic Syntheses," **26**, 78 (1946).

The **methiodide** was recrystallized from absolute alcohol–ether and melted at 233–234° with shrinking at 212°.

Anal. Calcd. for $C_{18}H_{27}O_2N_2I$: C, 50.23; H, 6.32. Found: C, 50.28; H, 6.03.

1-Ethyl-1-carboxy-3-dimethylamino-7-acetoxy-8-hydroxy-1,2,3,4-tetrahydronaphthalene Lactone (Ib).—A solution of 6.4 g. of the amine IX in 40 ml. of 48% hydrobromic acid was boiled vigorously under reflux for forty minutes. The excess hydrobromic acid was distilled at reduced pressure, leaving a brown crystalline residue. To this was added 20 ml. of acetic anhydride and 8.0 g. of anhydrous sodium acetate. The mixture was heated under reflux for two and one-half hours; it was then cooled, diluted with 100 ml. of ethyl acetate, and the sodium salts removed by filtration. The ethyl acetate was distilled, and the acetic anhydride and acetic acid removed by distillation under reduced pressure. The residue was evaporatively distilled at 155–165° (0.1 mm.). There was obtained 4.3 g. (64%) of a very viscous oil. The compound was not stable and it was not possible to obtain material of the desired degree of purity.

Anal. Calcd. for $C_{17}H_{21}O_4N$: C, 67.35; H, 6.98. Found: C, 66.63; H, 6.83.

This compound gave no derivatives with the exception of a **methiodide** which did not melt sharply. It was recrystallized from acetone and melted partially at 234°, decomposing at 250°.

Anal. Calcd. for $C_{18}H_{24}O_4NI$: C, 48.55; H, 5.43. Found: C, 48.95; H, 5.63.

On standing open to the atmosphere for one week the oil solidified to a colorless crystalline solid melting at 252–253° (dec.). This was purified by recrystallization from water, although some decomposition accompanied the process. Analysis of the solid indicated that hydrolysis of the lactone ring had taken place by absorption of atmospheric moisture and, indeed, it was later prepared more expeditiously by allowing the lactone to stand in the presence of water for twenty-four hours. Scission of the lactone ring in this way produced the amino-acid **1-ethyl-1-carboxy-3-dimethylamino-7-acetoxy-8-hydroxy-1,2,3,4-tetrahydronaphthalene (X).**

Anal. Calcd. for $C_{17}H_{23}O_5N$: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.77; H, 6.79; N, 4.39.

γ-Cyano-γ-(2,3-dimethoxyphenyl)-pimelonitrile (XI).—The procedure followed was that developed by Bruson[6] for the cyanoethylation of phenylacetonitrile. To a solution of 17.7 g. (0.1 mole) of 2,3-dimethoxyphenylacetonitrile[7] in 25 ml. of *t*-butyl alcohol containing 1.0 g. of 30% methyl alcoholic potassium hydroxide, was added, keeping the temperature at 10–25°, 12 g. of freshly distilled acrylonitrile dissolved in 10 ml. of *t*-butyl alcohol. The suspension, after the addition was complete, was stirred for two hours. The mixture was acidified with 5% hydrochloric acid, diluted with 100 ml. of water and the layers separated with the aid of benzene. Drying the extract over magnesium sulfate, followed by concentration, left 27.2 g. (96%) of a viscous oil which slowly crystallized to a solid melting at 60–63°. If the reaction mixture was allowed to stand until crystallization was complete, the product melted at 65–66°, but the yield was only 64%. Recrystallization from methanol–*t*-butyl alcohol did not change the melting point.

Anal. Calcd. for $C_{16}H_{17}O_2N_3$: C, 67.82; H, 6.05. Found: C, 67.86; H, 6.18.

2-Keto-3,3-di-(β-carboxyethyl)-7-methoxy-2,3-dihydrobenzofuran (XIX).—A solution of 3.0 g. of XI in 15 ml. of glacial acetic acid and 20 ml. of 48% hydrobromic acid was heated on the steam cone for one and one-half hours. The hot solution was chilled, diluted with 100 ml. of water and extracted with three 40-ml. portions of ethyl acetate. The extract was dried, concentrated and hexane was added until precipitation was complete. The supernatant liquid was decanted and the semi-solid residue taken up in hot water, treated with carbon, and the filtrate allowed to stand in the ice-box until crystallization was complete. The colorless crystalline solid weighed 1.6 g. and melted at 142–144°; the analytical sample melted at 148–149°.

Anal. Calcd. for $C_{16}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.38; H, 5.35.

The diacid chloride, prepared with thionyl chloride, was treated with stannic chloride in benzene solution in the usual way. No ketonic material could be isolated from the reaction mixture.

γ-Cyano-γ-(2,3-dimethoxyphenyl)-pimelic Acid (XII).—Best results were obtained when the trinitrile XI was recrystallized before use. Ten grams of the trinitrile (m. p. 65–66°) was dissolved in 100 ml. of absolute methanol and a rapid stream of dry hydrogen chloride passed into the solution for fifteen minutes. The mixture was heated gently under reflux for one hour and then one-half of the alcohol was removed by distillation. Dilution of the mixture with 150 ml. of water produced an oily precipitate which was separated with two 50-ml. portions of ether. After evaporation of the ether, the residue was heated under reflux for one hour with a solution of 6.0 g. of sodium hydroxide in 150 ml. of water and 15 ml. of ethanol. The cooled solution was extracted once with 30 ml. of ether and then acidified with 5% hydrochloric acid. The crystalline precipitate weighed 10.0 g. (88%) and melted at 177–178°. Two recrystallizations from hot water raised the melting point to 178–179°.

Anal. Calcd. for $C_{16}H_{19}O_6N$: C, 59.80; H, 5.96; neut. equiv., 161. Found: C, 59.97; H, 5.81; neut. equiv., 158.

This procedure for the hydrolysis of the trinitrile was adopted after direct hydrolysis failed to give the desired product.

1-Cyano-1-(β-carboxyethyl)-4-keto-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (XIII).—To a suspension of 25.5 g. of the acid XII in 100 ml. of absolute ether was added 20 ml. of thionyl chloride and 5 drops of pyridine. After standing two hours with occasional shaking, the mixture was heated for ten minutes on the steam cone to complete the reaction; by this time all material was in solution. The ether was distilled and the excess thionyl chloride removed at 50° at the water pump; 5 ml. of dry benzene was added and the operation repeated. The residue was dissolved in 400 ml. of dry thiophene-free benzene and the solution chilled until the benzene started to crystallize. Then 24 ml. of stannic chloride dissolved in 20 ml. of dry benzene was added with swirling, and the mixture allowed to stand in the ice-bath for one hour.[8] The mixture was poured upon a mixture of 50 ml. of concentrated hydrochloric acid, 50 ml. of alcohol-free ether and ice. When the yellow complex was destroyed, the organic layer was separated and washed with 5% hydrochloric acid, and twice with water. The extract was then heated under reflux with a solution of 12 g. of sodium hydroxide in 200 ml. of water. After cooling, the aqueous layer was run into 50 ml. of concentrated hydrochloric acid and ice. The precipitated acid weighed 19.5 g. (81%) and melted at 171–172°, after treatment with decolorizing carbon and recrystallization from dilute acetic acid.

Anal. Calcd. for $C_{16}H_{17}O_5N$: C, 63.36; H, 5.65. Found: C, 63.34; H, 5.46.

The colorless **oxime** melted at 185–186° (dec.) after recrystallization from dilute ethanol.

Anal. Calcd. for $C_{16}H_{18}O_5N_2$: C, 60.37; H, 5.70. Found: C, 60.44; H, 5.63.

1-Cyano-1-(β-carboxyethyl)-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (XIV).—In preliminary experiments on the catalytic reduction of one gram or smaller quantities of XIII, the products obtained were usually of better quality than larger scale runs. Occasionally the presence of a trace of hydrogen bromide appeared to give

(6) Bruson and Riener, *J. Am. Chem. Soc.*, **65**, 25 (1943).

(7) Horning, Horning and Platt, *ibid.*, **69**, 2929 (1947).

(8) This is essentially the general procedure in "Organic Reactions," Vol. II, 1945, p. 138.

products of high purity, but since this behavior was never consistent and poisoning of the catalyst always occurred, this method was abandoned. The course of the reaction is unknown, for it was impossible to isolate any intermediate that would be expected when half of the theoretical amount of hydrogen had been absorbed. Concentrated sulfuric acid was finally employed in conjunction with the palladium catalyst because somewhat purer products could be isolated than those formed in the absence of added acid.

Six drops of concentrated sulfuric acid were added to a suspension of 6.0 g. of XIII in 40 ml. of glacial acetic acid. Then 1.5 g. of 5% palladium–carbon catalyst[5] was added and the mixture hydrogenated at atmospheric pressure at 50–60°. In most cases, the end of the reaction was recognized only by a change in the rate of adsorption rather than a definite cessation. The catalyst was removed by filtration and the filtrate diluted with a slush of ice and water with vigorous stirring. The dried crystalline precipitate weighed 4.1 g. (72%) and melted at 108–112°. Purification for analysis was effected by recrystallization from dilute acetic acid. The pure acid melted at 123–124°.

Anal. Calcd. for $C_{16}H_{19}O_4N$: C, 66.42; H, 6.62. Found: C, 66.30; H, 6.48.

This acid was also obtained in small amount by a modification of the Wolff–Kishner reduction.[4] A mixture of 1.0 g. of XIII, 0.9 g. of potassium hydroxide, 0.9 ml. of 85% hydrazine hydrate and 15 ml. of diethylene glycol was heated at 145–150° for one hour. The temperature was gradually raised to 195° by allowing water vapor to escape from the reflux condenser. After one and one-half hours, the black solution was cooled, acidified with dilute hydrochloric acid and diluted with 50 ml. of water. It was then extracted with 100 ml. of ether and the extract shaken with 50 ml. of 5% sodium hydroxide solution. The alkaline solution was heated with carbon and the filtrate acidified with dilute hydrochloric acid. After standing in an ice-box for two days, the colorless needles were removed by filtration; the yield was 0.15 g., m. p. 119–120°. A recrystallized sample melted unchanged on admixture with that obtained by catalytic reduction.

In an effort to decrease the amount of carbonaceous material obtained in the reaction, the cyano group was first partially hydrolyzed by treatment with a mixture of concentrated hydrochloric acid and acetic acid. A solution of 5.0 g. of XIII in 25 ml. of concentrated hydrochloric acid and 25 ml. of glacial acetic acid was heated on the steam-bath for two hours. Within ten minutes the imide XVII started to crystallize from the reaction mixture. The mixture was cooled and the product filtered and washed, first with ethanol and finally with ether. The colorless crystalline solid weighed 4.5 g. (90%). The analytical sample was recrystallized from glacial acetic acid, m. p. 272–274° (dec.) (obtained in a melting block).

Anal. Calcd. for $C_{16}H_{17}O_5N$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.39; H, 5.46; N, 4.57.

The heterocyclic ring was cleaved by warming with dilute alkali until solution took place, followed by acidification with dilute hydrochloric acid. The amide-acid XVIII separated from ethanol or hot water in the form of colorless needles, m. p. 178–179°. Melting was accompanied by evolution of vapor and subsequent resolidification to regenerate the glutarimide XVII.

Anal. Calcd. for $C_{16}H_{19}O_6N$: C, 59.80; H, 5.96; neut. equiv., 321. Found: C, 59.67; H, 6.00; neut. equiv., 325.

Heating either the lactone-acid XIII or the imide XVII according to the Clemmensen method with a mixture of concentrated hydrochloric acid, acetic acid, zinc and toluene produced only impure materials which could not be purified. The Wolff–Kishner reaction carried out on XVII produced a small amount of amorphous material which could not be purified.

1-Cyano-1-(β-dimethylaminoethyl)-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (XV).—This compound was obtained in a manner analogous to that described for IX. From 3.34 g. of XIV (m. p. 108–112°) there was obtained by evaporative distillation at 120–125° (0.07 mm.); 1.4 g. (*ca.* 40%) of product as a pale yellow oil.

Anal. Calcd. for $C_{17}H_{24}O_2N_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.80; H, 8.05; N, 9.77.

The picrate separated from absolute ethanol–ethyl acetate in the form of lemon yellow leaflets, m. p. 180–181°.

Anal. Calcd. for $C_{17}H_{24}O_2N_2.C_6H_3O_7N_3$: C, 53.38; H, 5.26. Found: C, 53.52; H, 5.05.

Summary

The preparation of 1-ethyl-1-carboxy-3-dimethylamino - 7 - acetoxy - 8 - hydroxy - 1,2,3,4 - tetrahydronaphthalene lactone is described.

Experiments directed toward the synthesis of 1 - (β - dimethylaminoethyl) - 1 - carboxy - 7 - acetoxy - 8 - hydroxy - 1,2,3,4 - tetrahydronaphthalene lactone are also described.

Morphine Studies. The Synthesis of a Tetralin–Piperidine Fused-Ring System[1]

By R. U. Schock, Jr.[2]

One of the chief problems connected with the synthesis of morphine derivatives and morphine analogs lies in the synthesis of bridged-ring piperidine systems similar to that in morphine. This problem has been studied in a number of laboratories, and several methods have been found suitable for the preparation of certain types of analogs. A bicyclic system, containing a piperidine ring bridged at appropriate points, has been described recently by Cronyn.[3] Another bicyclic system involving a bridged-piperidine structure, in which the nitrogen was present in a quaternary salt group, was obtained by Barltrop,[4] and the method of synthesis was extended to the preparation of a tetralin analog. The synthesis of a compound (morphan) containing the carbon skeleton of morphine was recently announced by Grewe,[5] although experimental details of this work are lacking.

We have been interested in the preparation of certain tetralin analogs of morphine,[6] and in the course of the work it was necessary to investigate the problem of obtaining a tetralin–piperidine fused-ring system. At the same time, it was hoped that the investigation might result in a method sufficiently general to allow further application to the preparation of a synthetic tetrahydrodesoxycodeine. The work described here includes a study of two methods aimed at a ring system of the required sort.

The starting compound, 2,3-dimethoxyphenylacetonitrile, was alkylated with β-ethoxyethyl methanesulfonate to provide α-(2,3-dimethoxyphenyl)-γ-ethoxybutyronitrile (I). Addition of acrylonitrile led to the dinitrile II; this was converted into methyl γ-(2,3-dimethoxyphenyl)-γ-cyano-ε-ethoxycaproate (III) by means of hydrogen chloride in methanol. Formylation of the ester III with ethyl formate and sodium methoxide, followed by cyclization of the formyl derivative (IV) with sulfuric–phosphoric acids, gave the dihydronaphthalene derivative (V). Hydrolysis of the ester group, followed by hydrogenation with palladium–carbon catalyst in acetic acid, resulted in the tetralin derivative VI. The acid group was then transformed into the urethan group of compound VII through a method somewhat similar to that employed earlier,[6] except that ethanol was used during the Curtius rearrangement. Through the action of 48% hydrobromic acid under reflux, the crude urethan was converted into an amine hydrobromide (VIII). The structure of this intermediate was evident from the results of cyclization experiments; preliminary trials aimed at isolating a pure sample of this salt were not successful, and in later experiments solutions of the salt were used directly for cyclization after clarification with decolorizing carbon. There are six functional group reactions, including cleavage of three ether groups, hydrolysis of the cyano group, and hydrolysis-decarboxylation of the ester group, which occur at this point.

Cyclization of the intermediate was best carried out in aqueous solution in the presence of sodium acetate at *p*H 5. The resulting product was isolated as a crystalline acetyl derivative by acetylation in a solution maintained at *p*H 7–8 with sodium bicarbonate. The crystalline product was obtained in pure form without difficulty, and analytical data indicated that the empirical formula corresponded to a diacetyl derivative (IXb). The acetylation of only one phenol group in the parent compound, IXa, under acetylation conditions, is not without analogy in the morphine series. At the same time, the possibility that cyclization might have occurred to yield a chroman, with subsequent acetylation to provide the diacetyl derivative X, was also present. Freshly prepared solutions of the product gave an azo dye when treated with diazotized aniline or diazotized sulfanilic acid; this indicates the presence of a free phenolic group. The alternate assumption, that the compound is a chroman in which the acetyl group is hydrolyzed on contact with aqueous alkali, followed by *o*-coupling, appears far less probable.

A second method of synthesis was carried to the point indicated in the accompanying figure. It was hoped that the nitrosoketone could be reduced by the methods of Rosenmund[7] and Kindler.[7] Unfortunately, the nitrosation gave as a product an unstable oil from which very little crystalline material could be isolated.

The application of reaction methods leading to the formation of a tetralin–piperidine system are of particular interest in connection with a synthesis of tetrahydrodesoxycodeine. A useful precursor, 2-(2′,3′,-dimethoxyphenyl)-2-(β-ethoxyethyl)-cyclohexanone, has been prepared,[8] and work in this direction is under way.

(1) Abstracted from the dissertation of R. U. Schock, Jr., presented to the faculty of the Graduate School of the University of Pennsylvania in partial fulfilment of the requirements for the degree of Doctor of Philosophy, April, 1948.

(2) Bristol Laboratories Fellow, 1946–1947. National Institute of Health Predoctorate Fellow, U. S. Public Health Service, 1947–1948. Present address: The Abbott Research Laboratories, North Chicago, Illinois.

(3) Cronyn, Paper 87 of the Division of Organic Chemistry, American Chemical Society Meeting, April, 1948.

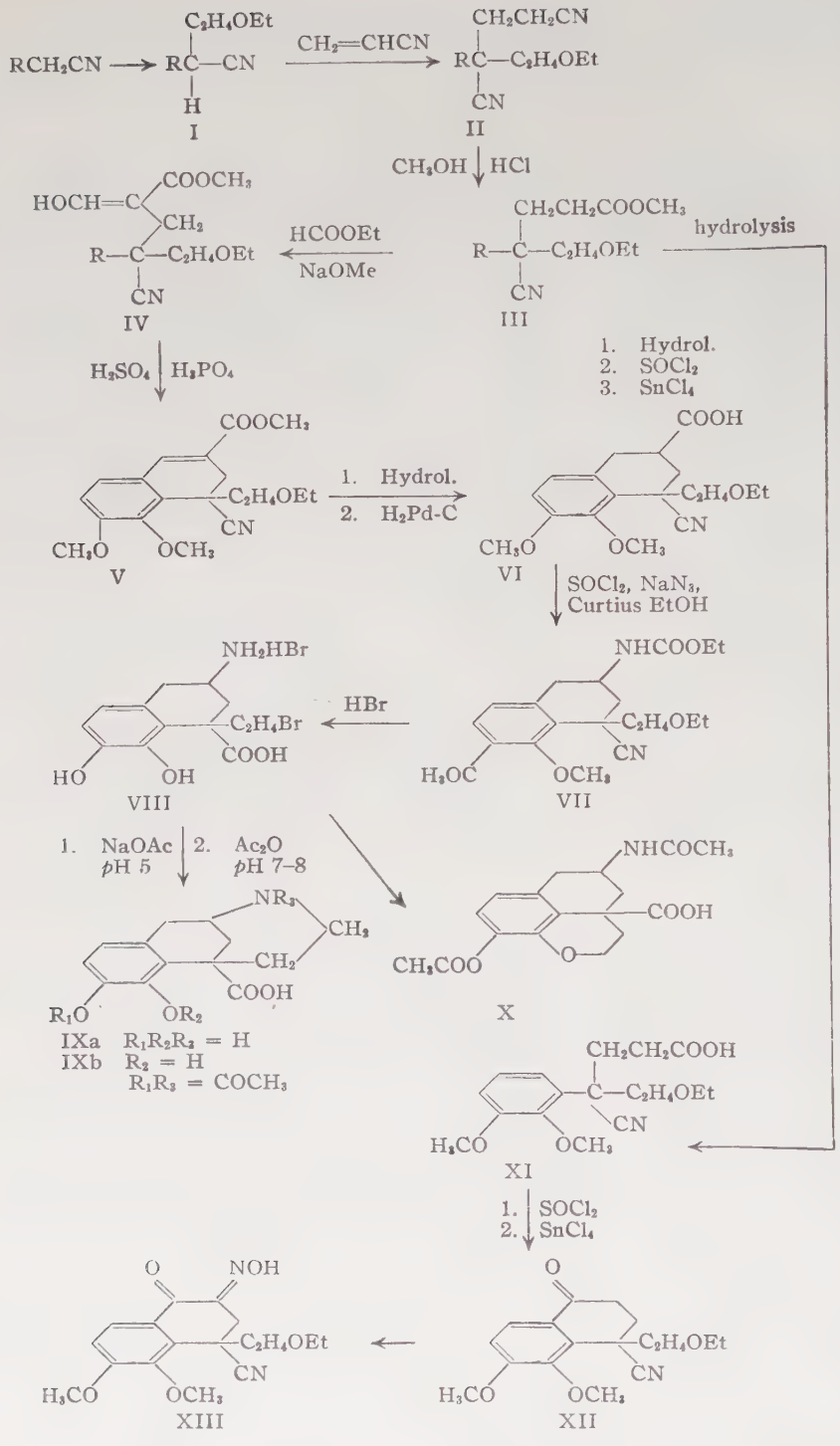
(4) Barltrop, *J. Chem. Soc.*, 399 (1947).

(5) Grewe, *Naturwiss.*, **11**, 333 (1946).

(6) Horning and Schock, *J. Am. Chem. Soc.*, **70**, 2941, 2945 (1948).

(7) Rosenmund and Karg, *Ber.*, **75**, 1850 (1943); Kindler and Dschi-yin Kwok, *Ann.*, **554**, 9 (1943).

(8) Horning, Horning and Platt, *J. Am. Chem. Soc.*, **70**, 2072 (1948).



Acknowledgment.—We are indebted to Mrs. Sarah Miles Woods for the analytical data.

Experimental

All melting points are corrected.

α-(2,3-Dimethoxyphenyl)-γ-ethoxybutyronitrile (I).—Sodamide was prepared from the reaction of 12.7 g. of sodium (0.55 mole) and 400 ml. of liquid ammonia in the presence of a trace of ferric nitrate.[9] A solution of 88.5 g. (0.50 mole) of 2,3-dimethoxyphenylacetonitrile in 100 ml. of dry benzene and 100 ml. of dry ether was added to the suspension of sodamide in liquid ammonia. The suspension was stirred for one hour or until the ammonia evaporated. Then, with vigorous stirring, a mixture of 92.4 g. (0.55 mole) of β-ethoxyethyl methanesulfonate[10] and 100 ml. of dry ether was added at such a rate that the heat of reaction maintained the mixture at gentle reflux. After heating under reflux for one hour, the mixture was cooled and diluted with 500 ml. of water. The layers were separated and the aqueous phase extracted once with 100 ml. of ether. The combined organic solutions were washed successively with 5% sodium hydroxide solution, 5% hydrochloric acid and with water. The extract was dried over magnesium sulfate, the solvents removed by distillation and the residue fractionated through a short Vigreux column. The fraction boiling at 131–140° (0.4 mm.) was collected. The yield of nearly colorless product was 105.2 g. (84%).

Anal. Calcd. for $C_{14}H_{19}O_3N$: C, 67.45; H, 7.68. Found: C, 67.48; H, 7.63.

α-(β-Ethoxyethyl)-α-(2,3-dimethoxyphenyl)-glutaronitrile (II).—The procedure followed was essentially that described by Bruson[11] for the cyanoethylation of phenylacetonitrile. A solution of 105.2 g. of the nitrile I in 90 ml. of *t*-butyl alcohol was heated to 40° and then, with stirring, the dropwise addition of a solution of 24 g. of acrylonitrile in 30 ml. of *t*-butyl alcohol was started. After the addition of a few drops, 2 ml. of a 30% aqueous solution of benzyltrimethylammonium hydroxide was added, and the temperature maintained at 40–45° by occasional external cooling. Another 2-ml. portion of catalyst was introduced after half the acrylonitrile was added. When the temperature no longer rose spontaneously, the solution was heated for one hour at 40–45° and allowed to stand overnight. The dark solution was acidified with dilute hydrochloric acid and diluted with 250 ml. of cold water. The layers were separated with the aid of ether and the aqueous layer extracted once with 50 ml. of ether. The combined extracts were washed with water and dried over magnesium sulfate. Distillation of the residue remaining after evaporation of

(9) "Organic Syntheses," **25**, 25 (1945).

(10) Newman and Magerlein, *J. Am. Chem. Soc.*, **68**, 942 (1947).

(11) Bruson and Riener, *ibid.*, **65**, 25 (1943).

the solvent yielded 108.5 g. (85%) of a colorless viscous oil boiling at 171–178° (0.3 mm.).

Anal. Calcd. for $C_{17}H_{22}O_5N_2$: C, 67.53; H, 7.33. Found: C, 67.68; H, 7.24.

Methyl γ-(2,3-Dimethoxyphenyl)-γ-cyano-ε-ethoxycaproate (III).—A solution of 108.5 g. of the dinitrile II in 400 ml. of absolute methanol was treated with a stream of dry hydrogen chloride for thirty minutes. The mixture was heated gently under reflux for one hour, and then approximately one-half the alcohol was removed in a current of air. Dilution of the cooled residue with water produced an oil which was separated by three 100-ml. portions of ether. The extract was washed with water, once with 50 ml. of saturated sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the solvent left a colorless residue which was distilled at reduced pressure. The fraction boiling at 176–180° (0.5 mm.) was collected; the yield was 104.7 g. (87%).

Anal. Calcd. for $C_{18}H_{25}O_5N$: C, 64.46; H, 7.51. Found: C, 64.51; H, 7.37.

γ-(2,3-Dimethoxyphenyl)-γ-cyano-ε-ethoxycaproic Acid (XI).—The ester-nitrile was hydrolyzed with aqueous alkali. It was found that greater yields were obtained if the intermediate ester was not distilled, but was saponified immediately after distillation of the solvent ether. Thus, the methyl ester obtained from 70.0 g. of the dinitrile II was boiled under reflux for two and one-half hours with a solution of 18 g. of sodium hydroxide in a mixture of 400 ml. of water and 10 ml. of ethanol. Upon acidification of the cooled alkaline solution with dilute hydrochloric acid, a colorless oil precipitated which was separated with two 75-ml. portions of ether. The extract was dried over magnesium sulfate and the ether distilled, leaving 72.7 g. (97%) of an oily residue. The product, γ-(2,3-dimethoxyphenyl)-γ-cyano-ε-ethoxycaproic acid XI, did not crystallize on standing and was not purified further. Derivatives prepared for characterization could not be crystallized.

1-Cyano-1-(β-ethoxyethyl)-7,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthoic Acid (VI). A. Formylation.—Sodium methoxide was prepared from 4.6 g. of sodium (0.2 mole) and absolute methanol. Then, at room temperature, a solution of 33.5 g. of the nitrile-ester III (0.1 mole) and 14.8 g. of ethyl formate (0.2 mole) in 100 ml. of dry ether was added to a vigorously stirred suspension of the sodium methoxide in 100 ml. of dry ether. After one and one-half hours, an additional 0.2 mole of ethyl formate was added and the stirring continued for another hour, at which time all suspended material was in solution. The solution was allowed to stand for fifteen hours; then 200 ml. of cold water was added and the layers separated. The aqueous layer was washed once with 50 ml. of ether and this extract combined with the original organic layer. From this ether solution there was obtained 5.6 g. of unchanged III which was pure enough for further use. The aqueous layer was acidified with dilute acetic acid and extracted with two 75-ml. portions of ether. The extract was washed once with 50 ml. of saturated sodium bicarbonate solution, dried, and the solvent evaporated. There was obtained 29.2 g. of the formyl derivative, as a pale yellow oil. The yield was 80% or 97% based on unrecovered nitrile-ester.

B. Cyclization.—A solution of 64.7 g. of the formyl derivative in 60 ml. of glacial acetic acid was added to a mixture of 175 ml. of 85% phosphoric acid and 45 ml. of concentrated sulfuric acid, keeping the temperature below 0°. The solution was allowed to stand at −5° for thirty minutes and 1.5 hours at room temperature. Pouring upon ice produced a viscous gum which was separated with three 100-ml. portions of ether. The extract was washed once with 75 ml. of 5% sodium hydroxide solution and then concentrated. The residue was heated under reflux for one and one-half hours with a solution of 16 g. of sodium hydroxide in 600 ml. of water and 20 ml. of ethanol. Acidification of the hot solution produced a gum which crystallized after standing twenty-four hours in an ice-chest. The dried crystalline **1-cyano-1-(β-ethoxyethyl)-7,8-dimethoxy-3,4-dihydro-3-naphthoic acid** melted at 165–166° and weighed 55.2 g. (93%). Recrystallization from dilute acetic acid raised the melting point to 167–168°.

Anal. Calcd. for $C_{18}H_{21}O_5N$: C, 65.24; H, 6.39. Found: C, 65.31; H, 6.35.

C. Reduction.—A solution of 17.0 g. of the acid in 150 ml. of glacial acetic acid was hydrogenated in a low-pressure apparatus in the presence of 5% palladium-carbon catalyst at 65°. The catalyst was removed by filtration and the filtrate concentrated in a current of air on a steam cone. The crystalline residue was fractionally crystallized from dilute acetic acid in an effort to isolate each of two possible diastereoisomers. The melting points of three crops (*ca.* 129–131°) were almost the same, and the filtrates yielded a compound which was apparently identical with that obtained in the first three crops but less pure. It is believed that one isomer is formed exclusively. Recrystallization raised the melting point to 131–132°. The yield of VI was 17.0 g.

Anal. Calcd. for $C_{18}H_{23}O_5N$: C, 64.84; H, 6.95. Found: C, 64.75; H, 6.76.

Conversion of VI to 1-Carboxy-3,1-acetyliminoethano-7-acetoxy-8-hydroxy-1,2,3,4-tetrahydronaphthalene (IXb).—A mixture of 2 ml. of thionyl chloride and 1.65 g. of VI was allowed to stand overnight. The excess thionyl chloride was removed at 50° at the water pump and the residual acid chloride taken up in 25 ml. of dry reagent-grade acetone. The solution was chilled in an ice-bath, and a solution of 0.73 g. of sodium azide in 2 ml. of water was added with vigorous stirring. After fifteen minutes the mixture was diluted with 75 ml. of cold water and the crude azide separated with three 25-ml. portions of ether. The extracts were washed once with sa urated sodium bicarbonate solution and dried for fifteen minutes over magnesium sulfate. To the ether extract was added 25 ml. of absolute ethanol and the solution slowly distilled on a steam cone through a short column. The residue of the **ethyl urethan** weighed 1.8 g. (95%). The residue was then boiled vigorously under reflux with 20 ml. of 48% hydrobromic acid for four hours, allowing the initial volatile products of reaction to escape from the reflux condenser. The dark solution was diluted with 50 ml. of hot water, treated with carbon and the colorless filtrate made slightly alkaline with solid sodium bicarbonate. Dilute hydrochloric acid was then added until the filtrate was acid. The acidified filtrate was boiled under reflux with 5.0 g. of sodium acetate trihydrate for 1.5 hours; the addition of sodium acetate brought the *p*H to approximately 5. The cooled solution was then treated with 2 ml. of acetic anhydride and solid sodium bicarbonate was added with stirring to keep the mixture alkaline (*p*H 7–8). After fifteen minutes, a further 2-ml. portion of acetic anhydride was added. After an additional fifteen minutes, the solution was acidified with dilute hydrochloric acid and extracted with four 25-ml. portions of chloroform. The combined extracts were dried over magnesium sulfate and evaporated, leaving a crystalline residue weighing 1.50 g. This material was purified by recrystallization from dilute acetic acid. The melting point of the pure compound varied from 258 to 262° (dec.) depending upon the rate of heating of the bath.

Anal. Calcd. for $C_{17}H_{19}O_6N$: C, 61.25; H, 5.74; N, 4.22. Found: C, 61.21; H, 5.68; N, 4.26.

Structure IXb, with the phenolic hydroxyl group acetylated (*viz.*, $C_{19}H_{21}O_7N$) requires: C, 60.79; H, 5.64; N, 3.73.

The presence of a phenolic group in this product was indicated by the addition of either diazotized sulfanilic acid or diazotized aniline to a freshly prepared alkaline solution of the compound; a deep orange color resulted. A small amount of the azo dye from diazotized *p*-nitroaniline was isolated in solid form, but it proved difficult to purify and was not characterized further.

4-Cyano-4-(β-ethoxyethyl)-5,6-dimethoxytetralone-1 (XII).—A solution of 63.0 g. of crude γ-(2,3-dimethoxyphenyl)-γ-cyano-ε-ethoxycaproic acid (XI) in 50 ml. of

absolute ether was treated with 30 ml. of thionyl chloride and three drops of pyridine. After standing for fifteen hours, the volatile constituents were removed at 50° at the water pump; 5 ml. of dry benzene was added and the operation repeated. The residue was dissolved in 600 ml. of dry thiophene-free benzene and chilled until the solvent began to crystallize. Then a solution of 40 ml. of stannic chloride in 40 ml. of benzene was added rapidly with shaking and the mixture allowed to stand in the ice-bath for fifteen minutes. The yellow complex was destroyed by pouring upon a mixture of 50 ml. of ether, 100 ml. of concentrated hydrochloric acid, and ice. The organic layer was then separated and washed successively with 5% hydrochloric acid, water, 5% sodium hydroxide solution, and finally with water. Drying, followed by evaporation of the solvent, left an oil which was distilled at reduced pressure. The fraction boiling at 192–198° (0.4 mm.) was collected as product; the yield was 42.2 g. (71%). The pale yellow oil solidified on standing and melted at 67–68° after recrystallization from cyclohexane–petroleum ether.

Anal. Calcd. for $C_{17}H_{21}O_4N$: C, 67.30; H, 6.98. Found: C, 67.14; H, 6.89.

Nitrosation of the Tetralone XII.—Various conditions and methods were tried without good results. Nitrosation with an ester of nitrous acid in the presence of dry hydrogen chloride produced only resinous products. In the presence of sodium alkoxides with either freshly prepared butyl or isopropyl nitrite, small amounts of the desired oximinoketone XIII were obtained. The yields in all cases were too low to warrant continuance of the synthesis along this path. The following procedure is an example of a successful experiment. A solution of 1.5 g. (0.005 mole) of XII and 0.23 g. of sodium in 50 ml. of absolute ethanol was prepared. Then, 1.5 g. (0.0075 mole) of freshly prepared *n*-butyl nitrite was added, and the mixture was allowed to stand at 5° for two days. The alcohol solution was diluted with an equal volume of cold water and extracted twice with 30-ml. portions of ether. The aqueous layer was acidified with diluted hydrochloric acid and extracted three times with 30-ml. portions of ether. Drying, followed by evaporation of the solvent, left 1.5 g. of a red oil which partially solidified on standing. Trituration with ether provided 0.15 g. of pale yellow **2-nitroso-4-cyano-4-(β-ethoxyethyl)-5,6-dimethoxytetralone-1 (XIII)** which melted with darkening at 154–155° after three recrystallizations from ethyl acetate–petroleum ether.

Anal. Calcd. for $C_{17}H_{20}O_6N_2$: C, 61.43; H, 6.07. Found: C, 61.33; H, 5.81.

Summary

A method leading to a compound containing a fused-ring tetralin–piperidine system, similar to part of the morphine ring system, has been developed.